REMARKS

Claims 88-100 were pending in this application. Claims 97-100 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 88-96 are under examination.

The applicants have noted the Examiner's objection to the oath and a new oath will be supplied. In addition, the Examiner objected to the Abstract for not completely describing the claimed invention. Applicants submit herewith a substitute Abstract. Applicants contend that the substitute Abstract fully describes the claimed invention and thereby complies with the Examiner's request. Applicants respectfully request entry of this substitute Abstract.

The Examiner noted certain trademarks. The specification has been amended to show the proper use of the trademarks. Applicants submit that the generic terminology is already used in the specification, where available. Attached are website printouts showing that Opti-MEM® and Lipofectin® are the uses of these terms by the corporation (Exhibit A).

Claims 88-96 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of related U.S. Patent No. 6,803,453. Applicant will file a terminal disclaimer upon indication of otherwise allowable subject matter in this application.

REJECTIONS UNDER 35 U.S.C. § 112 FIRST PARAGRAPH

Claims 88-96 are rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly is not enabling for an antibody to a protein variant encoded by SEQ ID NOs:1, 5, 9, 11, 13, or 15 or complements thereof, or a sequence having at least 90% identity to a full length sequence. The Examiner has cited publications authored by Bowie et al., Geysen et al., and Colman in support of the rejection. Applicants respectively submit that the claims as amended are enabled under the standards set forth in In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

A specification is presumed to be enabling and the U.S. Patent and Trademark Office (PTO) has the burden of establishing a *prima facie* case of lack of enablement. See, In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976); In re Marzocchi, 169

U.S.P.Q. 367, 369-370 (C.C.P.A. 1971). To make a *prima facie* case of lack of enablement, the PTO must come forward with reasons, supported by the record as a whole, showing why the specification fails to enable one of ordinary skill in the art to make and use the claimed invention. In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). The mere fact that some experimentation is necessary does not negate enablement as long as undue experimentation is not required. See M.P.E.P. § 608.01(p).

The burden is on the PTO to establish that experimentation would be undue, Angstadt, 190 U.S.P.Q. at 219, taking into consideration the eight factors that are to be considered in determining whether a disclosure requires undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the amount of experimentation which may be required to practice the present invention does not rise to the level of being undue experimentation, as defined by the Court in Wands.

An important aspect of the Court's decision in Wands is its finding that the nature of the technology pertinent to the Wands invention (monoclonal antibody production) permitted a broad definition of the term "experiment." The Court found that an "experiment" in the monoclonal antibody art consisted of the entire attempt to make a monoclonal antibody against a particular antigen. As described by the Court, the process entailed, "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." 8 U.S.P.Q.2d at 1407. Thus, Wands supports the conclusion that in a complex field such as monoclonal antibody production, the entire attempt to achieve the desired result, from beginning to end, constitutes one experiment.

According to the Court, repetition of this whole experiment more than once does not constitute undue experimentation. As the Court indicated, practitioners in the art would be prepared to screen negative hybridomas in order to find a hybridoma capable of making the desired antibody. 8 U.S.P.Q.2d at 1406. Thus, the fact that some aspects of the experiment as a whole will yield negative results does not mandate a finding that the amount of experimentation to achieve a positive result is undue.

Like the production of monoclonal antibodies, the identification or production of an antibody falling within the scope of the present claims may require some experimentation, but if viewed in the light of Wands, this experimentation, and the possibility of encountering negative results along the path to the positive results, is not undue. Furthermore, the present applicants provide extensive guidance to allow one of ordinary skill in the art to obtain an antibody that is within the scope of the claims.

Applying this information to the eight Wands factors, one of skill in the art would conclude that undue experimentation would not be required to practice the claimed invention.

1. *Quantity of experimentation necessary.* To obtain an antibody within the scope of the claims, the only experimentation required is the performance of known procedures for measuring binding of an antibody to an antigen. These procedures are routine and would not have to be done repeatedly before a definitive result was obtained. Because the inventors and the art provide means for the objective measurement of an antibody falling within the claim scope, this factor is met, for example, by the ability to test the binding of an antigen encoded by a polynucleotide that is at least 90% identical to SEQ ID NOs:1, 5, 9, 11, 13, or 15 or complements thereof.

The Wands court found that practitioners in the art are prepared to screen negative hybridomas to find one that made the desired antibody. (U.S.P.Q.2d at 1406.) The court further stated that an "experiment" was not simply the screening of a simple hybridoma, but instead was the entire attempt to make a monoclonal antibody against a particular antigen. This process included immunizing animals, fusing lymphocytes from the immunized animals to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas. (U.S.P.Q.2d at 1406).

By analogy, a single experiment in the present art could include obtaining or constructing a polypeptide encoded by a polynucleotide as recited in the claims, and measuring the binding of an antibody to this polypeptide. Encountering negative results would not mean that undue experimentation is involved, according to Wands.

2. *Amount of direction or guidance provided.* The specification provides clear directions for performing the experimentation, and cites to published scientific

articles for details not mentioned in the specification. Similarly, the Wands court found that the starting material was available to the public (as is the material used in the present application) and the patent application at issue in Wands provided a detailed description of the methods, which included use of a commercially available kit. (8 U.S.P.Q.2d at 1404, 1405).

3. *Presence or absence of working examples.* As a working example, the specification describes the preparation of antigens as well as the production and testing of antibodies. (Page 70, line 28 through page 72, line 29.)

4. *Nature of the invention.* The invention relates to antibodies. Methods of producing and testing antibodies are common knowledge in the biotechnology industry. The nature of the invention is such that it is well-known to those of ordinary skill in the art. The court in Wands stated that the nature of monoclonal antibody technology is that it involves screening, including screening of negative samples (in that case, hybridomas). The number of potentially negative samples was not viewed as a determining factor in reaching a finding of undue experimentation (8 U.S.P.Q.2d at 1406-1407).

5. *The state of the prior art.* The prior art provides the methods and materials needed to apply the methods of factor (4) above to this group of polypeptides. The Wands court found that "all the methods needed to practice the invention were well-known." (8 U.S.P.Q.2d at 1406). Similarly, the methods of producing and testing antibodies specific for peptide antigens are well known.

6. *The relative skill of those in the art.* Those of skill in this art are highly skilled and would be competent at designing and performing, or directing the performance of, the procedures of factors (4) and (5) above. The Wands court found that the level of skill in the monoclonal antibody art was high at the time the application was filed, but, importantly, the court found that development of skill in performing specific experiments relevant to the art did not preclude enablement. Specifically, the court stated that initial failures occurred as the inventors learned to fuse cells, and "[o]nce they became skilled in the art, they invariably obtained numerous hybridomas ..." that met the claim limitations. (8 U.S.P.Q.2d at 1406). By analogy, it would not

defeat enablement for one of skill in the art of antibody production to learn and become proficient in techniques for practicing the present invention.

7. *The predictability or unpredictability of the art.* One of skill, being acquainted with the methods described in the application, would predict that when routine procedures are used to modify the codons in SEQ ID NOs:1, 5, 9, 11, 13, or 15 corresponding to amino acid changes in polypeptides that bind to the claimed antibodies, polypeptides can be expressed that will bind to an antibody falling within the scope of the claims, and this can be routinely confirmed by antibody binding assays.

In Wands, the Court noted that the cell fusion technique was well known to those of ordinary skill in the art, and that there was no indication that the fusion step should be more difficult or unreliable for the antigen in question (HBsAg) than for other antigens. The Examiner has provided no evidence that the antibody binding assay steps would be "more difficult or unreliable" (8 U.S.P.Q.2d at 1406) for polypeptides encoded by polynucleotides that are 90% identical to SEQ ID NOs:1, 5, 9, 11, 13, or 15, or that hybridize to one of those polynucleotides.

8. *The breadth of the claims.* Using materials and methods routinely available at the time of filing, one of skill can routinely identify or construct any antibody molecule meeting the limitations of the claims, and test it for binding to polypeptides encoded by polynucleotides that are at least 90% identical SEQ ID NOs:1, 5, 9, 11, 13, or 15, or that hybridize to one of those polynucleotides.

The Bowie et al. (*Science* 247:1306-1310, 1990) reference cited by the Examiner relates to protein sequences and their tolerance to amino acid substitutions. The Geysen et al. (*J. Mol. Recog.* 1:32-41, 1988) and Colman (*Res. in Imm.* 145:33-36, 1994) references relate to antigen/antibody interactions and the effects of amino acid substitutions. All three references suggest that some amino acid substitutions affect proper folding of proteins and/or antibody/antigen binding, while many substitutions have no effect on protein folding or antibody/antigen binding. In particular, Bowie et al. states that "At some positions, many different nonconservative substitutions were allowed. Such residue positions play little or no role and structure and function." (Page 1306, column 2, paragraph 2). Regarding antibody/antigen interactions, the Geysen reference states in the Abstract that "It was found that on average only about four to five

amino acid residues in epitopes were required to determine specificity and provide binding energy." The Colman reference states that "Structural studies show that some non-conservative changes are tolerated at these interfaces." (Page 33, column 1, paragraph 1).

All three references support the conclusion that many substitutions in the antigen encoded by polynucleotides having at least 90% identity to SEQ ID NOs:1, 5, 9, 11, 13, and 15 are possible without affecting protein folding or antigen binding properties. Determining whether antigen amino acid substitutions resulting from variations in the polynucleotide sequences encoded by SEQ ID NOs:1, 5, 9, 11, 13, and 15 affected antibody binding would not be undue experimentation for the reasons outlined above.

In view of the foregoing remarks, applicants submit that the Examiner has not met his burden of making a *prima facie* showing that undue experimentation is required in order to practice the invention as claimed. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 88-96 are rejected under 35 U.S.C. § 112 first paragraph as failing to comply with the written description requirement. The Examiner states that the claims contain "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that inventor(s), at the time the application was file, had possession of the claimed invention". The applicants respectfully traverse this ground for rejection and submit that the instant application satisfies the written description requirements of 35 U.S.C. § 112.

The case cited by the Examiner, University of California v. Eli Lilly and Co., 119 F3d 1559, 43 U.S.P.Q.2d 1398, 1406 (1997), is not on point for the present fact pattern. The patent application at issue in Lilly disclosed a rat sequence for insulin, and contained one constructive example of how to obtain human sequence, but provided no disclosure of which amino acids to substitute, add or delete from the rat sequence to obtain the human sequence. In contrast, the present invention does teach a disclosed sequence and a finite number of variants thereof, all of which can be written down using the disclosed sequence.

The Court in Lilly stated, "Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a

description of that material." (43 U.S.P.Q. 2d at 1568.) That statement is not applicable to the present situation, where the material, the polynucleotides specified by SEQ ID NOs:1, 5, 9, 11, 13, and 15 are specifically known to exist, and so a situation involving the absence of knowledge as to what that material consists of simply is not applicable to the present invention.

The Lilly case presented a situation in which the applicants claimed a nucleotide sequence from one species, but they disclosed a polynucleotide sequence from a different species, and the application did not suggest specific amino acid substitutions, additions or deletions in order to derive the second polynucleotide sequence from the first. The court specifically declined to apply this reasoning to a situation such as the present one. "We will not speculate in what other ways a broad genus of genetic material may be properly described, but it is clear to us, as it was to the district court, that the claimed genera of vertebrate and mammal cDNA are not described by the general language of the 525 patent's written description supported only by the specific nucleotide sequence of rat insulin." (43 U.S.P.Q. at 1569.) Thus, the Lilly case does not support a position that disclosure of a specific polynucleotide sequence fails to provide written description for variants of that same polynucleotide sequence.

The Federal Circuit recently interpreted Lilly in a decision involving written description of a polynucleotide sequence, in Capon v. Eshhar, Slip Op. 03-1480, -1481 (Fed. Cir. August 12, 2005). The parties argued that precedent did not establish a *per se* rule requiring nucleotide-by-nucleotide re-analysis when the structure of the component DNA segments was already known or readily determined by known procedures. The Court agreed, stating that, among other cases, Lilly did not require a re-description of what is already known. Further, the Court held that the state of scientific knowledge must be considered.

The goal of the written description requirement is to prevent applicants from claiming priority to earlier applications if the current application discloses new matter not present in the earlier applications (Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Further, In re Kaslow affirms that "the test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at the

time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language" (707 F.2d 1366, 1375 (Fed. Cir. 1983)). Applicants submit that the claimed subject matter is fully supported by the specification of the current application.

REJECTION UNDER 35 U.S.C. § 102

The Examiner has rejected claims 88-96 under 35 U.S.C. § 102(b), asserting that U.S. Patent No. 5,453,492 ("the '492 patent") anticipates the subject matter of the claims. In particular, the Action alleges that the cited patent "teaches antibodies (monoclonal, polyclonal, or humanized) having specific reactivity with the TGF-β binding protein and hybridomas for producing an antibody." To support the rejection, the Examiner has cited publications by Bost et al. (*Imm. Invest.* 17:577-586, 1988) and Bendayan et al. (*J. Histochem. Cytochem.* 43:881-886, 1995), which both discuss the ability of antibodies to cross-react with peptide sequences from distinct proteins.

The Examiner concedes that '492 is silent with respect to the amino acid sequence of the TGF-β-1 binding protein described therein, and with respect to any nucleotide sequence encoding such protein. The Examiner asserts, however, that the amino acid sequences recited in the instant application are "inherently present in the referenced TGF-β binding protein as they were obtained from the same source." (Page 11.)

Applicants respectfully traverse these grounds for rejection. The Examiner has failed to establish a *prima facie* case of anticipation under 35 U.S.C. § 102(b) because no evidence or reasoning has been presented by the Examiner to show that antibodies which bind to the TGF-β-1 binding protein of '492 include any antibodies which specifically bind to a TGF-β binding protein according to the present invention, nor has the Examiner proffered any extrinsic evidence to show that the TGF-β-1 binding protein of '492 must *necessarily* be encoded by a polynucleotide as recited in claims 88-96.

Applicants respectfully submit that it is well known in the art that both the TGF-β protein superfamily, and the distinct family of TGF-β binding proteins, are extensive and highly varied, such that absent any showing to the contrary by the Examiner, there would be no reason for a person skilled in the art to believe that antibodies that bind to

the TGF-β-1 binding protein according to '492 would necessarily also bind to a TGF-β binding protein according to the presently claimed invention. For the Examiner's convenience, applicants submit herewith a copy of Balemans et al. (*Dev. Biol.* 250:231, 2002, Exhibit B), an exemplary recent review article which is not prior art but which summarizes the diversity in structures, cell and tissue origins, and binding specificities of binding proteins that interact with one or more members of the highly diverse TGF-β superfamily (see, e.g., Balemans et al. at pp. 235-244, including disclosure pertaining to "sclerostin," an alternative nomenclature used for the "Beer" proteins described in the present application).

In the present specification (e.g., page 12, lines 21-23; page 13, lines 16-20; page 33, lines 8-11; and elsewhere) the subject matter encompassed by the instant claims is satisfactorily described, as the Examiner has previously conceded, and applicants respectfully submit that the skilled artisan would have no basis for concluding that the presently claimed subject matter is *necessarily* coextensive in scope with any antibody disclosed in '492. Accordingly, the Examiner has failed to meet the burden of establishing that the subject matter of the presently claimed invention is inherently present in '492.

M.P.E.P § 2112 provides that:

> In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. *Ex parte Levy*, 17 USPQ2d 1461, 1464 (BPAI 1990) (emphasis in original).

Accordingly, applicants submit that the burden remains with the Examiner to supply the requisite basis in fact and/or technical reasoning, where mere conjecture on the part of the Examiner does not suffice as a finding that the prior art reference contains a disclosure that anticipates the presently claimed invention. Furthermore, the Examiner has offered no evidence making clear that "the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." (Continental Can Co. USA v. Monsanto Co.,948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991) (M.P.E.P. § 2131.01 (III)).

It is axiomatic that for a cited reference to anticipate a claimed invention, each and every limitation of the claim must be present in a single reference. Applicants therefore submit that the Examiner has failed to meet the burden of supplying extrinsic evidence to supplement the incomplete disclosure of '492, and that the Examiner therefore cannot demonstrate that an antibody of '492 *necessarily* must bind to a TGF-β binding protein as recited according to the instant claims. Accordingly, no *prima facie* case of anticipation under 35 U.S.C. § 102(b) has been established, and applicants respectfully request that the rejection be withdrawn.

If fees are believed necessary, the Commissioner is authorized to charge any required fee, deficiency or credit any overpayment to Deposit Account No. 04-0258. A duplicate copy of this document is enclosed.

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
Mary E. Brunkow et al.
DAVIS WRIGHT TREMAINE LLP

By _____
Jane E. R. Potter
Registration No. 33,332

2600 Century Square
1501 Fourth Avenue
Seattle, WA 98101-1688
Phone: (206) 628-7650
Facsimile: (206) 628-7699